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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,525	10/14/2005	Athina Markou	TSRI 897.1	3218

26621 7590 01/08/2009

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EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
01/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,525	MARKOU ET AL.	
	Examiner	Art Unit	
	KENDRA D. CARTER	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,14-17,19 and 27-33* is/are pending in the application.

4a) Of the above claim(s) *10,14,15,17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,16,20-22 and 27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and declaration of September 26, 2008 made to the office action filed June 3, 2008. Claims 1-10, 14-17, 19 and 27-33 are pending. Claims 20-26 are canceled and claims 10, 14, 15, 17 and 19 are withdrawn.

For the reasons in the previous office action and below, the Applicant's arguments of the following 35 U.S.C. 103(a) rejections were found not persuasive, thus the rejection is upheld: 1) claims 1-8, 16, 20, 21 and 29 as being unpatentable over Adam et al. in view of Corsi et al. or Chimulera et al.; 2) claims 9, 22, 27, 28, 32 and 33 as being unpatentable over Chiamulera et al. in view of Adam et al. as applied to claims 1-8, 16, 18, 20, 21 and 29 above; 3) claims 29, 30, 31 and 33 as being unpatentable over Bear et al. in view of Adam et al.

The Examiner would like to clarify that the 35 USC 102(b) rejection of claims 1-5, 20 and 21 as being anticipated by Fudytus et al. was withdrawn in the previous action.

Due to the Applicant's arguments not being persuasive and no new amendments to the claims, the previous 35 U.S.C. 103(a) rejections are made below. Applicant's arguments and declaration are addressed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

(1) Claims 1-8, 16, 20, 21 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adam et al. (US 6407,094 B1) in view of Corsi et al. (US 2003/0195139 A1) or Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874).

Adam et al. teaches compounds that act as Group II (i.e. mGluR 2 and 3) metaboltropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions which lead to glutamate-deficiency functions such as nicotine addiction, opiate addiction, anxiety and depression (see column 1, lines 54-56 and column 3, lines 20-24; addresses claims 1-8, 16, 20, 21 and 29). The antagonist can be in their pharmaceutically acceptable salts (see column 3, line 4).

Adam et al. does not teach an antagonist which modulated metabotropic glutamate receptor 5, or its administration in combination with the antagonist of Adam et al.

Corsi et al. teaches a method of treating substance dependence, wherein the substance is nicotine, opiate, cocaine, amphetamine, benzodiazepine and ethanol, comprising administering a therapeutically effective amount of an antagonist of mGluR5 (see claims 21-23; addresses claims 1-7, 20, 21, 27, 29 and 30). Depression and anxiety is also treated (see page 7, paragraph 119, line 7; addresses claims 1-3, 8, 29 and 30). The compounds can be in the form of salts (see page 3, paragraph 55, lines 1 and 2).

Chiamulera et al. teaches the significant contribution of mGlu5 receptors to the behavioral effects of cocaine addiction (see page 873, column 1, paragraph 1, last 4 lines). A decrease of self-administration of cocaine was observed with an

administration of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP); see page 873, column 2, last paragraph, lines 1-4).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Adam et al. and a combination with an antagonist which modulates metabotropic glutamate receptor 5 because of the following: (1) Adam et al., Corsi et al., and Chiamulera et al. teach methods that treat addictive disorders or depression; (2) Adam et al. teaches the treatment of addictive disorders, depression or/and anxiety with a mGluR 2 and 3 antagonist; and (3) Corsi et al. and Chiamulera et al. teach the treatment of an addictive disorder or depression with a mGluR 5 antagonist. One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat addictive disorders, depression or and/anxiety. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

(2) Claims 9, 22, 27, 28, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874) in view of Adam et al. (US 6,407,094 B1) as applied to claims 1-8, 16, 20, 21 and 29 above.

The teachings of Chiamulera et al. and Adam et al. all are as applied to claims 1-8, 16, 20, 21 and 29 above.

Chiamulera et al. and Adam et al. do not teach the antagonist 2S-2-amino-2-(1S,2S-2carboxycyclopropane-1-yl)-3-(xanth-9-yl)propionic acid (LY341495; claims 22 and 28). Also, the administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression, is not taught (claim 27). Lastly, wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously is also not taught (claims 32 and 33)

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and the antagonist LY341495 because of the following: (1) both Chiamulera et. al. and Adam et al. teach methods to treat substance abuse; (2) Adam et al. teaches the treatment of an addictive disorders or depression with a mGluR 2 and 3 antagonist; and (3) LY341495 is a well known mGluR 2 and 3 antagonist in the art (indicated by the specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4). One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat substance abuse. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and an administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5

(specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression; or (c) wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously because without unexpected results, one skilled in the art can reasonably design the period of administration.

(3) Claims 29, 30, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bear et al. (US 6,916,821 B2) in view of Adam et al. (US 6407,094 B1).

Bear et al. teaches a method of treating anxiety comprising administering an effective amount of the Group I mGluR antagonist (i.e. mGluR 1 and 5), 2-methyl-6-(phenylethynyl)-pyridine (MPEP; see claims 1 and 2).

Bear et al. does not teach the antagonist LY341495. Also, a method wherein an antagonist of metabotropic glutamate receptor 2 and metabotropic glutamate receptor 3 (specifically LY341495) is administered when the subject experiences depression symptoms, and an antagonist of metabotropic glutamate receptor 5 (specifically MPEP)

is administered when the subject experiences anxiety symptoms is not taught. Lastly, wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously is also not taught (claim 33).

Adam et al. teaches compounds that act as Group II (i.e. mGluR 2 and 3) metaboltropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions which lead to glutamate-deficiency functions such as nicotine addiction, opiate addiction, anxiety and depression (see column 1, lines 54-56 and column 3, lines 20-24).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Bear et al. and the antagonist LY341495 because of the following: (1) Bear et al. teaches a method of treating anxiety with the mGluR 5 antagonist MPEP; (2) Adam et al. teaches a method of treating depression and anxiety with a mGluR 2 and 3 antagonist; and (3) LY341495 is a well known mGluR 2 and 3 antagonist in the art (indicated by the specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4). One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat addictive disorders or depression. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for

the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and an administration comprising: an antagonist of metabotropic glutamate receptor 2 and metabotropic glutamate receptor 3 administered when the subject experiences depression symptoms, and an antagonist of metabotropic glutamate receptor 5 administered when the subject experiences anxiety symptoms; or wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously, because without unexpected results, one skilled in the art can reasonably design the period of administration.

Response to Arguments

Declaration

> The Declaration of Dr. Markou teaches that prior to the subject invention, it would not be obvious to combine a mGluR2/R3 antagonist and a mGluR5 antagonist to treat addictive disorders. The localization of mGluR2/3 and mGluR5 receptors indicate that antagonist actions of the mGluR2/3 increase glutamate transmission, while antagonist actions at the postsynaptic mGluR5 decrease glutamate transmission. There are a

number of references from the literature that suggest that one should expect opposite neurochemical and behavioral effects of a mGluR2/R3 antagonist and a mGluR5 antagonist. For instance, Mills et al. teaches the mGluR5 antagonist MPEP decreased excitatory amino acid concentrations, while treatment with the mGluR2/3 agonist LY 341495 increased excitatory amino acid levels. Xi et al. teaches that mGluR2/3 antagonist LY 143495 increases extracellular glutamate, while Thomas et al. teaches that the mGluR5 antagonist MPEP inhibited glutamate release. Sharko et al. teaches that the mGluR5 antagonist MPEP significantly enhanced both the sedative and hypnotic effects of ethanol, while the mGluR2/3 antagonist LY341495 significantly decreased the sedative hypnotic effects of ethanol.

Further, substance abuse and substance dependence are related but different concepts that may usually require different means for treatment and intervention.

Lastly, Fundytus et al. does not disclose treatment of withdrawal symptoms but that MCPG prevents the development of morphine dependence. Fundytus et al. reports that treatment with mGluR antagonist has no effect on withdrawal symptoms that have already developed morphine dependence (see page 1018, left column).

The Examiner has considered the declaration but does not find it persuasive to overcome the rejections. First, one would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat substance abuse, depression, and/or anxiety and are known glutamate antagonist. Second, Mills et al. teaches that the Group II mGluR2/3 antagonist LY 341495 is administered 5 min prior through 15 min post injury (i.e. prevention; see page 843, column 1, first full paragraph, lines 1-3). In contrast, when the Group II and Group III antagonist CPPG is given, the glutamate was decreased versus increased (see page 842, column 1, first full paragraph, lines 1-10). Third, Xi et al. also teaches that mGluR2/3 antagonist LY 143495 and APICA increase glutamate, but when combined

with the mGluR2/3 agonist APDC, the glutamate was decreased (see Figure 2b and page 164, column 1, paragraph 4, lines 1-8). Forth, Thomas teaches that the mGluR1 agonist DHPG increases glutamate, but the mGluR5 antagonist MPEP decreases glutamate. When DHPG and MPEP are combined the glutamate is decreased (see Figure 1B). Thus, the amount of glutamate can be adjusted by adding different Groups as shown by Mills et al., or by adding different receptor agonist and/or antagonist as shown by Xi et al. and Thomas et al.

In regards to Sharko et al., Adam et al. has shown that a mGluR2/3 antagonist is effective in treating nicotine and opiate addiction. Further, Corsi et al. and Chimulera et al. teach that a mGluR5 antagonist, particularly MPEP, is effective in treating nicotine, opiate, cocaine, amphetamine and/or other substance dependence/addiction. Therefore, one skilled in the art would be motivated to combine to two type drugs in expectation that one could treat substance addiction (dependence). *"It is* prima facie *obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."* In re Kerkhoven, *626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also* In re Crockett, *279 F.2d 274, 126 USPQ 186 (CCPA 1960);* Ex parte Quadranti, *25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and* In re Geiger, *815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).* In other words, just because Sharko et al. teaches that mGluR2/3 and mGluR5 have opposite effects in

ethanol, Corsi et al., Chimulera et al. and Adam et al. teach that the same mGluR antagonists treat substance addiction. Therefore, the opposing activities as presented by the Applicant both still treat substance addiction.

In regards to Fundytus et al., when the mGluR antagonists were administered prior to withdrawal (i.e. prevention), there was no difference between vehicle-treated rats and mGluR antagonist treated rats (see page 1018, column 1 in its entirety). On the other hand, during the 40 min withdrawal period for morphine-dependent rats, the mGluR antagonist significantly decreased the frequency of counted symptoms compared to the vehicle-treated control group (see page 1017, column 1, paragraph 3 in its entirty, Figure 1b). Thus, the non-selective mGluR antagonist MCCG (at receptors 1, 2, 3, and 5) was effective in treating withdrawal symptoms. As stated in the previous rejection, the relationship between withdrawal symptoms and substance additions is evidenced by Bradley et al. (Addiction, 1987, vol. 82, no.10, pp. 1139-1142, particularly the abstract). Particularly, withdrawal symptoms are experienced by opiate addicts. Bradley et al. teaches that withdrawal symptoms are feared by many addicts and according to behavioral models, provide negative reinforcement for continued drug taking. Furthermore, conditioning models emphasize the role of conditioned withdrawal in precipitating relapse (see abstract, lines 1-5). Thus, treating withdrawal applies to both individuals that are dependent or addicted to opiates, and thus Fundytus et al. provides a therapeutic effect (i.e. treating withdrawal) in treating an addictive disorder with a Group I and Group II mGluR.

Claims rejected under 35 U.S.C. 103

The Applicant argues the same points taught in the Declaration summarized above.

The Examiner disagrees for the reasons given above in response to the Declaration.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/K. D. C./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617